the fraction of Cep192 hydroxylated in mitosis was not investigated. Interestingly, mutation of this key proline residue (P1717A) in Cep192 led to decreased recruitment of PCM proteins in mitosis and prometaphase arrest with disorganized spindles, mimicking protein knockdown. Apart from a potential role in cell-cycle regulation of Cep192, any involvement of PHD1 in regulation of this protein should be reflected by cellular oxygen availability, and this is indeed the case: hypoxic conditions led to reduced PHD activity, with concomitant increases in Cep192 and HIF levels. Surprisingly, although iron chelation led to increased Cep192 abundance at centrosomes, hypoxia led to the opposite result, suggesting additional mechanisms that restrict Cep192 localization. To complete the circuit, the authors showed that proline hydroxylation of Cep192 triggered its association with the SCF^{Skp2} complex, leading to Cep192 ubiquitylation and destabilization, analogous to the relationship between HIF and VHL.

In aggregate, these findings indicate that PHD1 is required for proline hydroxylation of Cep192, which regulates the abundance and function of this protein, and this connection suggests a linkage between metabolic state, centrosome biogenesis, and cell-cycle progression. Of course, every novel discovery also raises manifold questions and prompts new avenues of exploration. First and foremost, does endogenous PHD1 localize to centrosomes under normoxic and anoxic conditions, and where does PHD1 function to hydroxylate its target? It is reasonable to speculate that there are additional targets within the centrosome, cilium, and mitotic spindle that could serve as substrates for PHD proteins and additional mechanisms that respond to hypoxia by acting on protein localization as well. This speculation is supported by the fact that only a small portion of Cep192 is modified, yet ablation of PHD1 has a profound impact on centrosomes and mitosis. Intriguingly, earlier studies in *Drosophila* suggested that the Mps1 kinase, which plays a role in the mitotic spindle checkpoint and mammalian centrosome duplication (Fisk and Winey, 2001), was required for hypoxia-mediated metaphase arrest (Fischer et al., 2004). Thus, it is possible that the links between centrosome function and metabolic states are highly conserved. Finally, overexpression of Cep192, like depletion of Cep192 or PHD1, was detrimental, as it diminished γ-tubulin recruitment and led to abnormal centriole numbers in mitosis. These results suggest that correct levels of Cep192 are critical for normal spindle assembly and warrant a detailed investigation into expression levels and mutations in human tumors.

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Slide to the Left and Slide to the Right: Motor Coordination in Neurons

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Molecular motors employ specific adaptor proteins to dock on transport cargos. Reporting in *The Journal of Cell Biology*, Fu and Holzbaur (2013) show that the adaptor JNK interacting protein 1 (JIP1) binds kinesin-1 and dynactin and controls bidirectional axonal amyloid precursor protein trafficking, suggesting a regulatory role for adaptors during cargo transport.

Kinesin and dynein motor proteins move directionally along microtubule tracks to drive long-range cargo transport. Because of their size and highly polarized structure, neurons rely heavily on this microtubule-based transport system. Defects in kinesin and dynein transport processes are thought to play a critical factor in the pathogenesis of many neurological diseases. Impairment of axonal transport, for instance, is a common factor in many neurodegenerative diseases

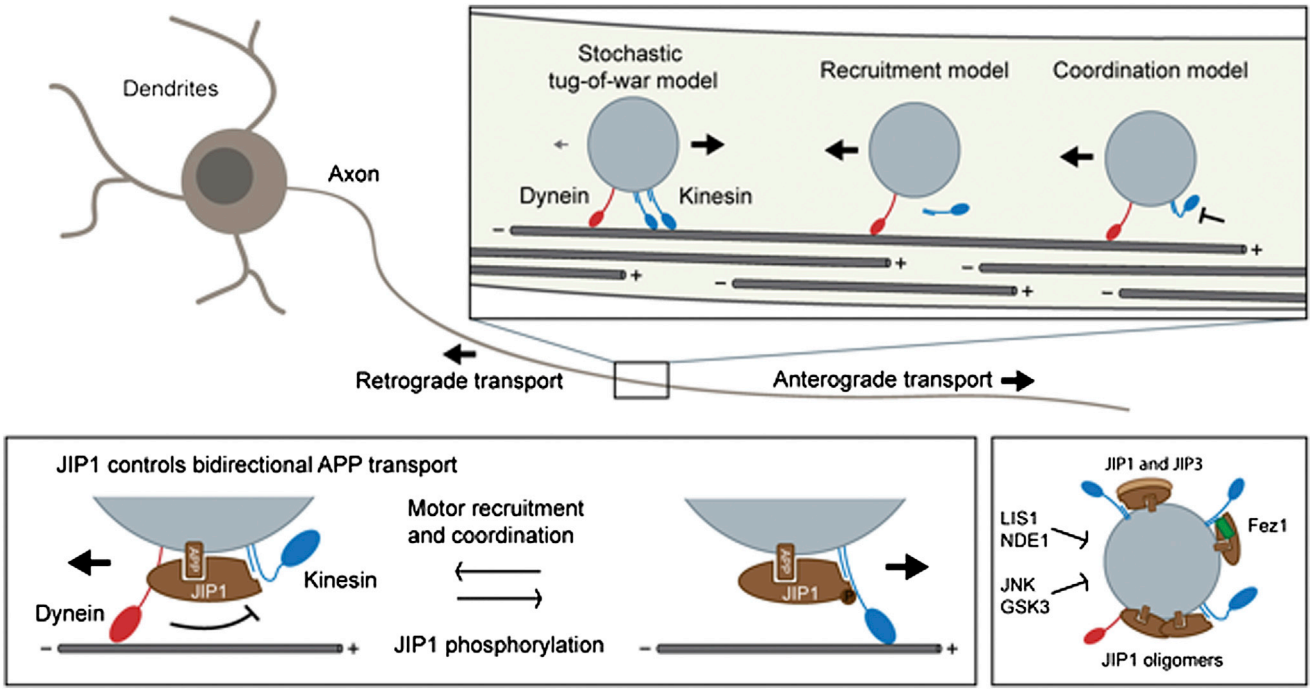

Figure 1. Models for Opposing Motor Coordination in Neurons
Top: microtubules within the axon have uniform polarity (plus end out) and serve as tracks for kinesin-dependent anterograde transport and dynein-dependent retrograde transport. Three models have been proposed to explain how opposing kinesin and dynein motor activity results in bidirectional movement. Tug-of-war model: stochastic binding of motors to the cargo results in bidirectional pulling forces followed by cargo movement in the direction of the strongest force. Recruitment model: kinesin or dynein is recruited to the cargo in a mutually exclusive manner. Coordination model: motor activity is regulated while bound to the cargo. Bottom left: model based on work by Fu and Holzbaur (2013), which is a combination of coordination and recruitment models. Bottom right: the JIP-motor complex could serve as an interaction hub for various signaling and regulatory molecules.

such as Alzheimer's disease. One of the best-known axonal cargos is the transmembrane amyloid precursor protein (APP), a precursor molecule whose cleavage product generates amyloid-β (Aβ), the primary component of amyloid plaques found in the brains of Alzheimer's disease patients. In axons, APP is transported in both anterograde and retrograde directions. Over the last few years, several models have been proposed for how this bidirectional motility is mediated by opposing motors on a single cargo to control the net direction of transport (Figure 1). Now, work published in *The Journal of Cell Biology* from Fu and Holzbaur (2013) finds that the cargo adaptor JIP1 functions to coordinate kinesin and dynein motor function for APP transport.

The c-*jun* N-terminal kinase (JNK)-interacting protein (JIP) family comprises four members that serve as scaffolding molecules for JNK signaling pathways. In addition, JIP1 and JIP3 function as cargo adaptors that link cargo (such as APP for JIP1) to kinesin-1 via its light chain (KLC) for axonal transport (Koushika, 2008). To investigate how JIP1 can influence APP transport in more detail, Fu and Holzbaur (2013) knocked down JIP1 in primary mouse dorsal root ganglion (DRG) sensory neurons and imaged fluorescently labeled APP in axons. Not only did JIP1-knockdown neurons display a marked reduction in the number of motile APP vesicles, but the vesicles that remain motile also exhibit a decrease in both anterograde and retrograde movements. To assess the mechanism of bidirectional APP transport, the authors first focused on testing the role of JIP1 in the kinesin-1 complex. Using in vitro motility assays, the authors demonstrate that JIP1 relieves autoinhibition of kinesin heavy chain (KHC) and enhances motor processivity. Because native kinesin-1 consists of two light chains and two heavy chains and because previous experiments showed that JIP1 is insufficient to activate KHC motility in the presence of KLC, additional regulatory factors such as fasciculation and elongation protein ζ1 (FEZ1) likely play crucial roles in regulating anterograde APP transport in neuronal cells (Blasius et al., 2007). Fu and Holzbaur (2013) also found that phosphorylation on serine 421 in JIP1 enhances KHC binding and promotes anterograde APP axonal transport. This is consistent with the JNK pathway, or other signaling factors such as glycogen synthase kinase 3 (GSK-3), in regulating APP transport (Weaver et al., 2013). In this way, the JIP1-motor complex could serve as an interaction hub for various signaling and regulatory molecules (Figure 1).

Several adaptor proteins, such as TRAK/Milton on the mitochondrial membrane, have been found to interact with both kinesin and dynein motors to control bidirectional transport (van Spronsen et al., 2013). So how does JIP1 regulate retrograde axonal transport in DRGs? Fu and Holzbaur (2013) tackled this question by performing a series of biochemical and in vitro motility experiments and found an interaction between JIP1 and the p150Glued subunit of the

dynein activator dynactin. JIP1 cannot form a tripartite complex with KHC and p150Glued, although it is able to interact simultaneously with KLC and p150Glued. The authors suggest that the JIP1 complex on APP vesicles exists in two mutually exclusive states. In one conformation, JIP1 binds directly to KHC in the absence of p150Glued to mediate anterograde transport. In the other conformation, JIP1 binds directly to KLC and p150Glued to mediate retrograde transport. In this conformation, KHC cannot directly bind to the p150Glued-JIP1 complex, but the binding of KLC may keep autoinhibited KHC docked on APP vesicles (Figure 1).

The model for JIP1 as a coordinator of axonal transport of APP raises many further questions. Are motors recruited to newly formed APP vesicles or is motor-cargo binding temporally controlled during the transport processes? In other words, does JIP1 play a role during the formation or maintenance of the functional transport complex? Recent data suggested that the kinesin-1 and dynein motors are stably bound on APP vesicles and that motor coordination, but not recruitment, leads to bidirectional motility along the microtubule (Reis et al., 2012). Another interesting addition to this discussion is a study by Lu and Prehoda (2013) in this issue of *Developmental Cell* showing that in cultured *Drosophila* S2 cells, NDE1, an important dynein regulator, and 14-3-3 adaptors connect kinesin-73 (Kif13B in mammals) and dynein to coordinate the activities of opposing motors in mitotic spindle orientation. Here, the authors propose a model in which inactive dynein is attached to the cortex. Kinesin-73 at the plus end of astral microtubules enters into the proximity of cortical dynein and delivers NudE, thereby activating dynein to generate cortical pulling forces. Although it remains unclear where dynein is positioned on APP vesicles and whether it is in an active or inactive conformation, p150Glued recruitment might similarly activate dynein on APP vesicles and stimulate retrograde axonal transport. Therefore, the attachment of dynein motors may not be essential in controlling bidirectional APP transport, but recruitment of dynein regulators, such as p150Glued/dynactin, could be a crucial step for coordinating motor activity.

It will be key for future work to resolve both the broader role of JIP1 in cargo transport and its sufficiency in the process. For instance, in *Drosophila* mutant for JIP1, synaptobrevin vesicles have anterograde and retrograde transport defects but mitochondria are only affected in the retrograde direction (Horiuchi et al., 2005). This suggests that JIP1 is an adaptor in other trafficking routes and controls transport by cargo-specific mechanisms. In terms of JIP1 sufficiency, however, in contrast to the findings of Fu and Holzbaur, (2013), it was recently shown that in cortical neurons, JIP1 loss does not affect APP transport (Vagnoni et al., 2013). These data suggest that other proteins, such as its close homolog JIP2, most likely compensate for the reduced JIP1 levels in this system. Although JIP3, another member of the protein family, is structurally unrelated to JIP1/JIP2 and does not directly bind to APP, it can form a complex with JIP1 and KLC and associates with dynein in *Caenorhabditis elegans* (Arimoto et al., 2011). In addition, JIP1 and JIP3 can both hetero- and homo-oligomerize and require each other for kinesin-1-mediated transport (Hammond et al., 2008), adding yet another layer of complexity to axonal APP transport (Figure 1). A better understanding of the precise composition and architecture of the APP-JIP-motor complex would provide important insight into the molecular mechanism of APP transport and clarify how disruption of APP function is associated with axonal transport defects in early Alzheimer's disease.

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